Tumors of the Kidney, Ureter, and Bladder

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Neoplastic processes involving the kidneys, the ureters, or the bladder account for 10% of all tumors in men and 4% of all tumors in women.[1]* Tumors of these organs represent a broad histologic range and vary widely in their clinical behavior. Despite this diversity, a common presenting feature of these lesions is either gross or microscopic hematuria. More than 85% of patients with uroepithelial neoplasia and 59% of patients with renal parenchymal tumors have this associated finding.[2,3] For this reason, a clear understanding of the evaluation of patients presenting with hematuria is germane to the discussion of tumors of these organs.

Evaluation of Microscopic Hematuria

Up to 13% of asymptomatic adult patients may present with microscopic hematuria.[4] Table 1 lists an abbreviated differential diagnosis for this common finding.[5] It is a clinician's responsibility to distinguish those patients with benign conditions from those with malignant urinary tract diseases. Because tumors of the urinary tract primarily affect the adult population, the following discussion will focus on this group of patients.

As with any disease, a thorough history and physical examination constitute the framework for further evaluation. Clearly the differential diagnosis in an elderly man with flank pain and a palpable flank mass will be different from that of a sexually active woman who presents with urinary frequency and urgency, despite the fact that both may have microscopic hematuria. Historical evaluation must include any record of urologic diseases and manipulation as well as any background of urinary tract infections, calculus disease, or previous neoplasms. A history of local or constitutional symptoms as well as previous traumatic injury must be sought. A complete physical examination with special attention to the abdomen, flanks, and external genitalia in men and a pelvic examination in women is essential.

The urinalysis should be repeated in all patients seen for microscopic hematuria. In the microscopic evaluation of the centrifuged urinary sediment, the presence of more than 1 to 3 erythrocytes per high-power field is considered an abnormal result.[6,7] The presence or absence of associated pyuria, bacteriuria, or proteinuria may be important in establishing the cause of hematuria. Red blood cell morphology may aid in distinguishing glomerular hematuria from that of more distant sites.[8,9] All patients with microscopic hematuria must have a urine culture.

Failure to establish a clear diagnosis at this point in the evaluation indicates the need for further study. The subsequent workup should include excretory urography or renal ultrasonography in combination with cystoscopy. Renal ultrasonography in combination with cystoscopy may be the most cost-effective strategy for evaluating asymptomatic microscopic hematuria, with a sensitivity and specificity identical to strategies that include excretory urography.[10] We prefer to do imaging studies of the upper urinary tract before cystoscopy because findings in the upper tract may influence the nature and extent of subsequent endoscopic evaluation. Filling defects in the upper urinary tract may warrant retrograde pyelography, upper tract cytology, or ureteropyeloscopy alone or in combination as part of the diagnostic evaluation.

Evaluation of Gross Hematuria

The discussion has so far been limited to asymptomatic patients who present with microscopic hematuria. In addition to the history, physical examination, urinalysis, and urine culture, all patients with gross hematuria or symptoms attributable to the urinary tract in association with microhematuria warrant excretory urography and cystoscopy. Only rarely will these diagnostic studies fail to establish a clear diagnosis in patients with gross hematuria. Historically, these unusual patients required interval evaluation with excretory urography and cystoscopy to preclude an occult malignant neoplasm. Recent advances in fiberoptic instrumentation, however, now enable urologists to visualize the upper urinary tract directly. Flexible ureteropyeloscopy is now established as an important diagnostic study in patients with otherwise unexplained gross hematuria.[11,12]

Patients With a Renal Mass

The diagnostic studies just outlined will identify a subset of patients with renal masses. In addition to patients identified as having hematuria, an increasing number of incidental renal masses are being discovered in patients undergoing diagnostic studies for other reasons. In the past, surgical exploration was often necessary to define the nature of a renal mass. Rapid advances in cross-sectional imaging techniques now enable the establishment of the diagnosis before a surgical procedure in more than 90% of all cases. This diagnosis often obviates the need for surgical intervention.

An algorithm for evaluating a patient with a renal mass is shown in Figure 1. The specific decision path depends on whether or not a renal mass is identified initially by ultrasonography or excretory urography. Computed tomography (CT) is warranted in patients whose excretory urogram shows a contrast-enhancing renal mass.

*See also "Tumors of the Urinary Tract," by Marc B. Garnick, MD, elsewhere in this issue (page 556).

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ABBREVIATIONS USED IN TEXT

BCG = bacillus Calmette-Guérin
CT = computed tomography
MRI = magnetic resonance imaging
PTH = parathyroid hormone
RCC = renal cell carcinoma

For nonenhancing masses identified by excretory urography, it is vital to differentiate solid from cystic lesions. Ultrasonography has proved highly sensitive—95% accurate—in this regard and is therefore the next diagnostic study. Lesions that fulfill the ultrasonographic criteria of simple cysts—peripheral location, smooth thin wall, absence of internal echoes, and posterior wall enhancement—require no further evaluation. Complex renal cysts or solid masses require further workup as indicated in the algorithm. On occasion, renal ultrasonography fails to identify a mass suspected on excretory urography. In these cases a dimercaptosuccinic acid (DMSA) isotope scan of the renal cortex or renal CT scan may aid in the evaluation.

A patient in whom the ultrasound study, obtained either initially or after excretory urography, demonstrates a solid or complex renal mass requires an abdominal CT scan. Contrast enhancement of a renal mass is an important feature of neoplasia. Sections should therefore be obtained through the area of interest both before and after the administration of intravenous contrast (Figures 2 and 3). Other CT findings may provide clues to the diagnosis. Angiomyolipomas are characterized as inhomogeneous masses with areas of low-density fat. Renal oncocytomas may demonstrate a central stellate scar.

In a patient with a suspected neoplasm, an abdominal CT scan also provides important staging information. The local extent of the lesion, status of the contralateral kidney, nodal enlargement, renal vein or vena caval involvement, and other sites of intra-abdominal metastasis may be defined using this technique. On rare occasions, additional imaging techniques may be necessary. In indeterminate cases (5% to 8%), renal arteriography, needle aspiration cytology, or cyst puncture may be needed to establish the diagnosis.

The role of magnetic resonance imaging (MRI) in evaluating renal mass lesions has yet to be defined. Early experience suggests that the ability of MRI to acquire primary data from multiple planes may be useful in local tumor staging—defining pararenal fat, para-aortic nodal and adjacent organ extension, and intravascular tumor thrombi (Figure 4).[13,14] The development of paramagnetic agents capable of contrast-like enhancement may expand the usefulness of MRI.[15]

Despite the impressive diagnostic armamentarium now available, it is occasionally impossible to establish a diagnosis. In these cases a decision between observation and surgical exploration must be made based on an assessment of the risks to an individual patient.

Benign Renal Tumors

Table 2 lists common renal tumors.[16] Any histologic component of the kidneys may be associated with benign neoplastic growth. Often the distinction between benign and malignant renal processes is based more on biologic behavior in a given patient than on histologic type. The best example of this is the so-called renal adenoma.

Renal Adenomas

Renal adenomas are the most common benign solid parenchymal lesions. By definition they are less than 3 cm and are often histologically indistinguishable from renal cell carcinoma (RCC). They tend to occur in circumstances similar to RCC in that they occur most frequently in patients older than 40 and have a 3:1 male-to-female ratio.[17(p435)] These lesions have been designated benign by some investigators based on the benign clinical course following surgical re-

TABLE 1.—*Causes of Hematuria**

Hematologic
Coagulopathy
Anticoagulation
Sickle cell anemia and trait
Sickle cell-thalassemia
Sickle cell-hemoglobin C disease

Renal (glomerular)
Acute proliferative glomerulonephritis (GN) (poststreptococcal GN)
Primary mesangiopathic GN (Berger's disease and other nonsystemic focal proliferative GN)
Focal proliferative GN associated with systemic disease (Henoch-Schönlein purpura, vasculitis)
Rapidly progressive GN (any cause)
Lupus nephritis
Membranoproliferative GN
Alport's syndrome
Benign familial hematuria
Any other glomerular lesion

Renal (nonglomerular)
Nephrosclerosis secondary to hypertension
Renal infarct
Renal vein thrombosis (infants)
Tuberculosis
Pyelonephritis
Polycystic disease
Medullary sponge kidney
Interstitial nephritis (drug allergy, infection)
Tumors
Vascular malformations
Trauma
Papillary necrosis
Cortical necrosis
Perirenal hematoma (infants)

Postrenal
Stones
Periureteritis secondary to extraurinary pathology
Tumors of lower urinary tract
Cystitis (schistosomal, bacterial, viral, drug-induced, radiation, idiopathic)
Prostatitis
Epididymitis
Meatal ulceration (circumcised boys)
Urethral stenosis
Foreign bodies of bladder or urethra (including Foley catheter)
Strenuous exercise
Urethritis
Phimosis
Benign prostatic hypertrophy
Obstruction
Vascular malformations
Endometriosis
Vesicoureteral reflux

False
Red diaper syndrome
Vaginal bleeding
Bleeding circumcision
Factitious
Pigmenturia
- Porphyria
- Hemoglobinuria
- Myoglobinuria
- Food—beets, blackberries, rhubarb
- Drugs

*Adapted from Abuelo.5

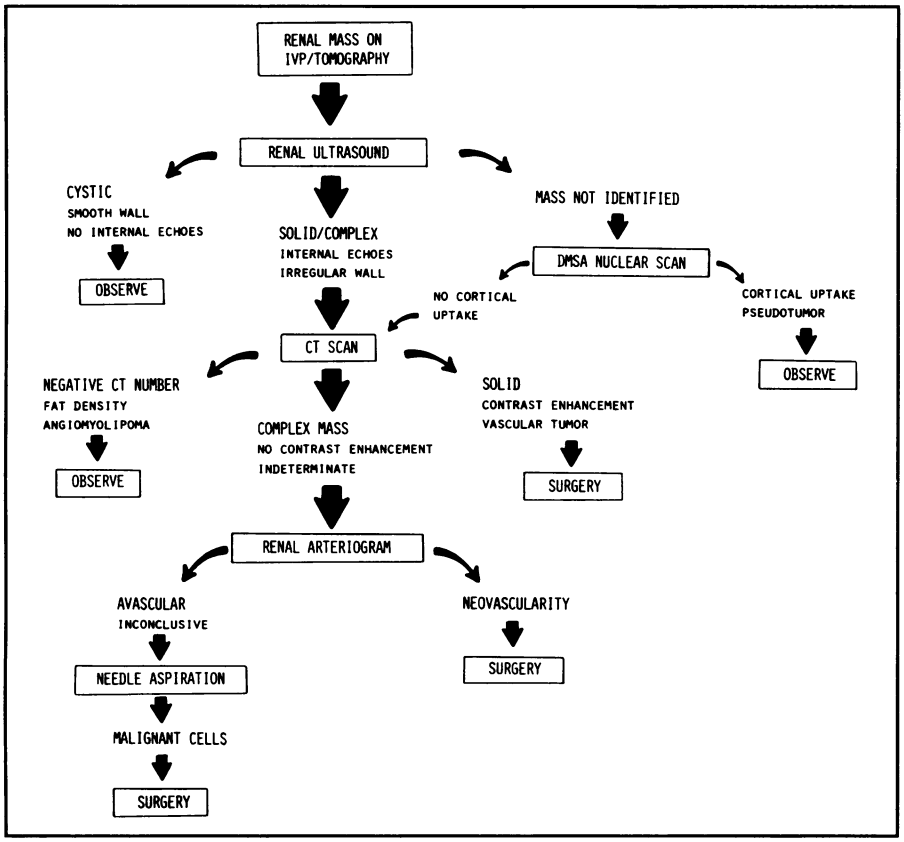


Figure 1.—An algorithm is presented for the evaluation of patients with suspected renal masses. CT = computed tomography, DMSA = dimercaptosuccinic acid, IVP = intravenous pyelogram

moval of the lesions. Renal adenomas have been reported to metastasize, however, and they should probably be considered to represent an early stage of RCC.[18] For this reason, current recommendations are for surgical removal. Although radical nephrectomy is usually advocated, trials of subtotal nephrectomy in highly selected patients have met with good results.[19]

Oncocytoma

Renal oncocytoma, a subtype of adenoma accounting for 5% to 7% of renal tumors, is indistinguishable preoperatively from renal adenoma and RCC. Classically, these lesions have a spoke-wheel pattern on the angiogram. This, however, is not sufficient to exclude a malignant lesion, and treatment continues to be radical nephrectomy. Renal oncocytomas have a pale brown appearance and histologically contain cells with an abundant acidophilic cytoplasm.

Angiomyolipoma

Hamartoma-angiomyolipoma is most often observed in conjunction with a diagnosis of tuberous sclerosis (adenoma sebaceum, epilepsy, and mental retardation).[20] These lesions tend to be multiple, synchronous, or metachronous and are commonly bilateral. As the name implies, they contain vas-

TABLE 2.—*Classification of Renal Neoplasms**

Benign
Adenoma
Oncocytoma
Angiomyolipoma/hamartoma
Fibroma
Leiomyoma
Lipoma
Hemangioma
Juxtaglomerular tumor

Primary malignant
Renal cell carcinoma
Urothelial—renal collecting system and pelvis—transitional cell, squamous cell, and adenocarcinoma
Sarcoma

Secondary malignant
Adrenal carcinoma
Retroperitoneal sarcoma, pancreas, colon (direct extension)
Lung, stomach, breast, prostate (hematogenous metastases)
Hematologic tumors—lymphoma, leukemia
Multiple myeloma (primary or metastatic)

*Adapted from Williams.[16]

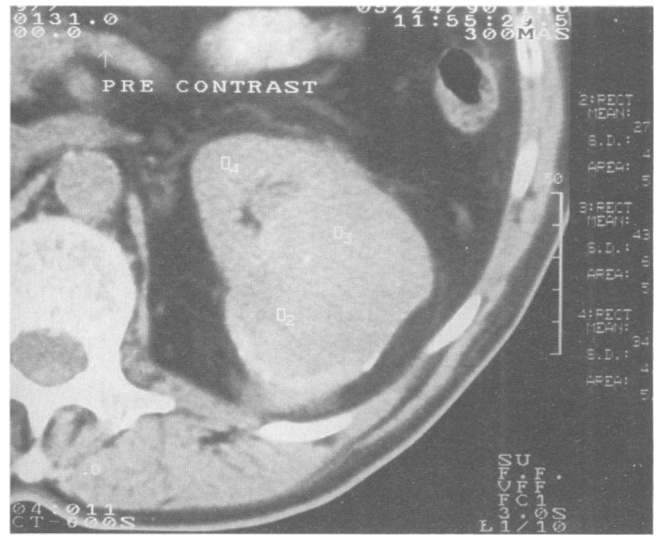


Figure 2.—Noncontrast-computed tomographic scan through a left renal mass lesion (O_2 and O_3) is shown.

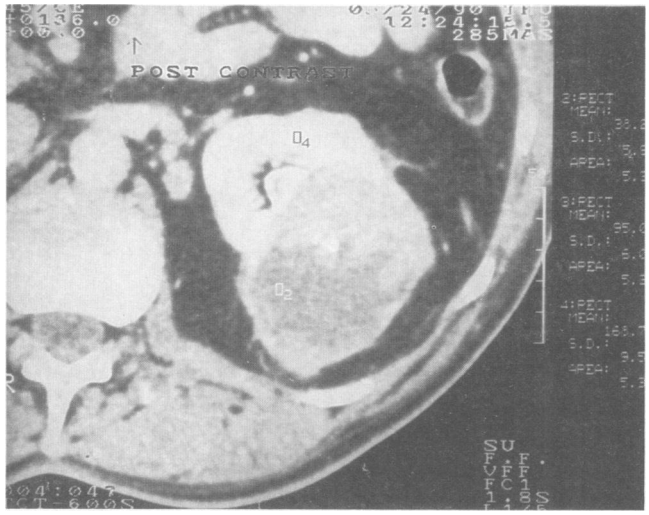


Figure 3.—A contrast-enhanced computed tomographic scan through the identical plane seen in Figure 2 shows the areas of contrast enhancement and tissue inhomogeneity characteristic of neovascularity and necrosis within the tumor (O_2).

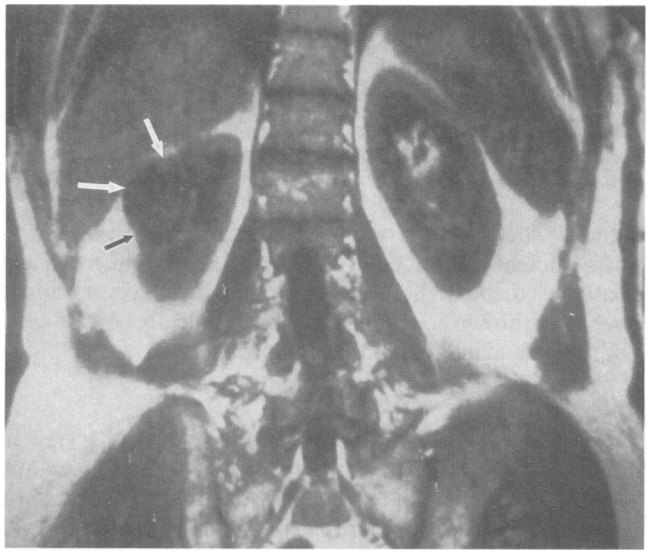


Figure 4.—A coronal T1-weighted magnetic resonance image through the right kidney shows a clear plane between the right renal mass lesion **(arrows)** and the liver.

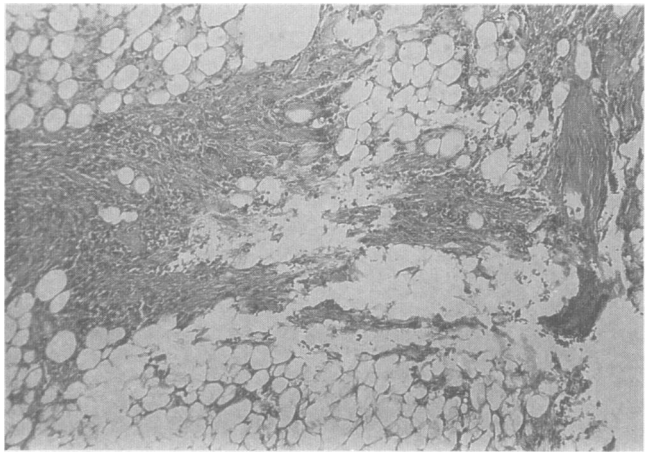


Figure 5.—Histologic examination of a renal angiomyolipoma shows prominent vascular and fat components (hematoxylin and eosin; original magnification × 63).

cular, adipose, and smooth muscle elements. Their vascularity may account for their common presentation with retroperitoneal hemorrhage (Figure 5).

In contrast to other neoplasms, angiomyolipoma can be diagnosed with a high degree of certainty using CT and ultrasonography. The fat content of the tumor, manifested as low-density areas on CT or highly echoic regions on ultrasound, may enable establishment of the diagnosis. Asymptomatic patients with these classic findings and small (< 5 cm) tumors, particularly associated with tuberous sclerosis, do not require a surgical procedure and have an excellent prognosis without treatment. The diagnosis may be more difficult to establish in patients without classic radiographic changes. When doubt exists, they should be surgically removed.

Acquired Renal Cystic Disease

Patients with end-stage renal disease are at risk of developing multiple bilateral cysts in the renal cortex as a direct function of the duration of their renal failure.[21] As many as two thirds of the patients on dialysis for four or more years have findings characteristic of this process.[22] The risk of cyst development appears to be independent of the type of dialysis.[23]

Of greatest concern in patients with acquired renal cysts is the risk of developing renal carcinoma. As many as 4% of patients with end-stage renal disease and acquired cystic disease have been noted to develop RCC.[24] As many as 9% of patients on long-term dialysis have been reported to have benign or malignant renal growths, an approximately 30-fold increase compared with azotemic patients not on dialysis.[25]

The true incidence of RCC in patients with acquired cystic disease is still undefined, but there does appear to be some increase relative to the normal population. For this reason we advocate baseline and interval ultrasonographic follow-up of all patients on dialysis. Our algorithm for the follow-up and management of such patients is shown in Figure 6.[26] Patients

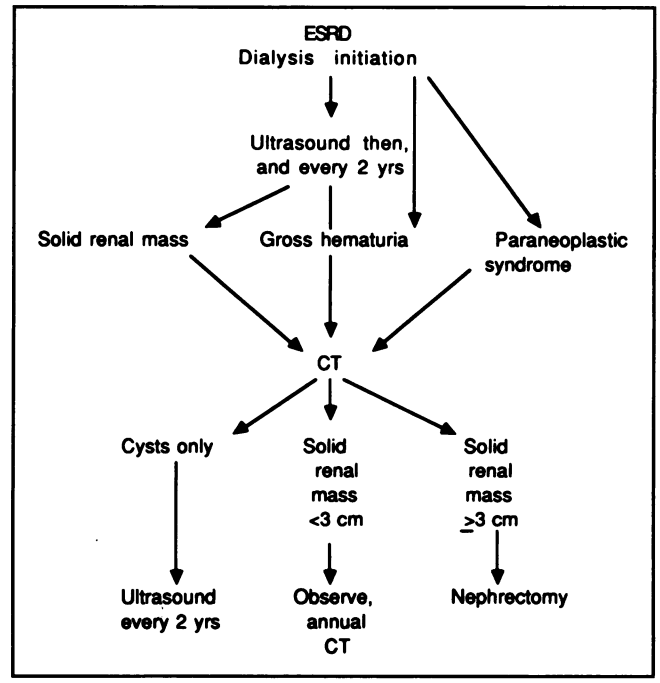


Figure 6.—An algorithm is presented for the follow-up of patients at risk for acquired renal cystic disease (from Fallon and Williams[26]). CT = computed tomography, ESRD = end-stage renal disease

with ultrasonographically detected solid renal masses or hematuria should undergo the evaluation described previously for these findings.

Xanthogranulomatous Pyelonephritis

Because of its tendency to mimic neoplastic processes, xanthogranulomatous pyelonephritis has been termed the great imitator.[27] Histologically, this is a destructive renal process resulting from chronic infection and inflammation. Normal renal parenchyma is replaced by inflammatory cells, histiocytes, and macrophages. This diagnosis should be suspected in patients with a history of chronic urinary tract infection (particularly with *Proteus* species) and persistent pyuria or bacteriuria, particularly in association with calculous disease of the kidney. Treatment consists of partial or total nephrectomy, depending on the extent of renal involvement.

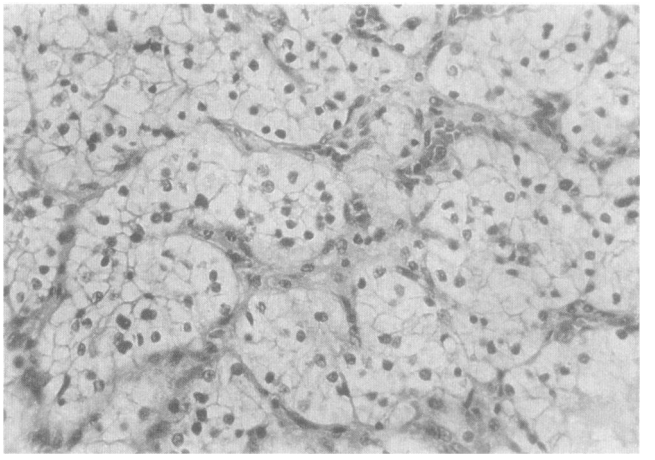
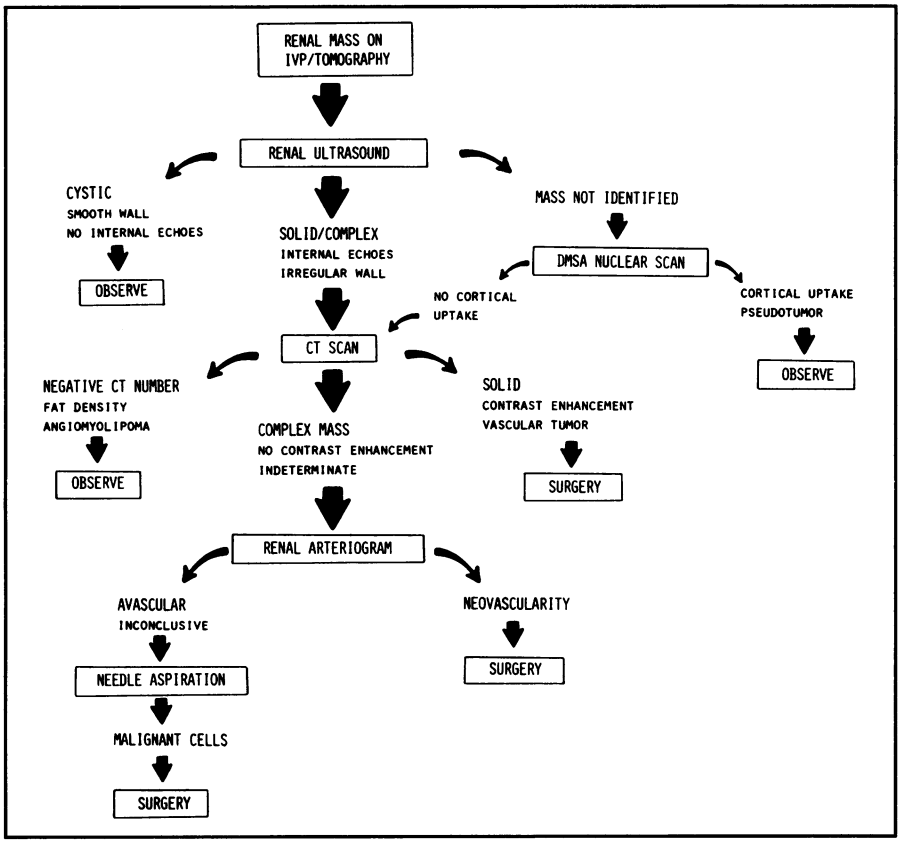


Figure 7.—Classic clear cell pattern of renal cell carcinoma is shown (hematoxylin and eosin; original magnification x 250).



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sine monophosphate. It was originally thought to be secondary to ectopic production of parathyroid hormone (PTH). The hypercalcemia has now clearly been shown to be secondary to secretion of a novel peptide hormone termed PTH-related protein, which has considerable homology to PTH in structure and in biologic activity.[36] The serum calcium level returns promptly to normal levels after successful removal of the RCC.

Nonmetastatic hepatopathy, also called the nephrogenic hepatic dysfunction syndrome or Stauffer's syndrome, describes a disorder of unknown pathogenesis and nonspecific hepatic histology in which hepatic function is deranged in patients with renal cell carcinoma. Most common are elevations of serum alkaline phosphatase and globulin levels with prolongation of both the prothrombin time and the excretion of sulfobromophthalein sodium. The serum albumin level is frequently reduced, and more rarely the aspartate aminotransferase level is increased. Hepatosplenomegaly may accompany these functional derangements, all of which return to within normal limits after surgical removal of the tumor. Hypertension in patients with an RCC may be "essential" and unrelated to the tumor or may be secondary to an increased production of renin. Anemia is frequently found and usually represents the anemia of chronic illness with decreased red blood cell survival and poor marrow responsiveness rather than iron loss from hematuria. More striking, however, is the erythrocytosis that occurs in 3% to 6% of patients, which is caused by the secretion of erythropoietin by the tumor. Renal cell carcinoma is one of the malignant tumors, like the lymphomas, that is most frequently associated with fever. The fever is often intermittent and is thought to result from the release of endogenous pyrogens from the tumor itself.

Rarely, RCC manifests first with the acute onset of a varicocele, especially in the left scrotum. The left gonadal vein normally drains into the left renal vein, where it may be obstructed by thrombosis or by direct extension of the tumor into the renal vein.

Diagnosis. There is no specific diagnostic laboratory test for RCC. The diagnosis must be considered in patients with unexplained constitutional symptoms or hematuria. The diagnostic evaluation relies on the algorithm described previously for the investigation of a renal mass or hematuria.

Therapy. Therapy is dictated by the stage of the disease. The TNM and Robson staging classifications are summarized in Figure 8.[37] The local extent of the disease is most commonly determined by CT scan, which must address direct local extension to other organs, lymphatic spread, and tumor extension into the renal vein or inferior vena cava. The functional status of the contralateral kidney is important in determining the therapeutic options. Hematologic metastatic tumor spread commonly involves the lungs, bones, or both. Routine staging should also include a chest radiograph, bone scan, and serum alkaline phosphatase measurement.

The treatment of patients with stage T1, N0, M0 through T4b, N0, M0 consists of radical nephrectomy, which by definition includes the removal of Gerota's fascia and its contents (kidney and adrenal gland) as well as the regional draining of the lymph nodes. The value of an extended lymphadenectomy in treating patients with occult nodal disease is currently an issue of debate.[38] A unique surgical dilemma that merits comment is the patient who presents with synchronous bilateral RCC or RCC in a solitary kidney. Recent experience indicates that parenchyma-sparing procedures are not only technically feasible but also provide excellent control of the neoplastic lesion.[39,40]

Prognosis. The pathologic tumor stage remains the most important predictor of survival rate.[41] The stage demonstrates a significant correlation with both nodal and distant metastatic involvement. These two indicators in turn are highly predictive.[42] Patients without nodal or metastatic involvement at the time of tumor removal have a five-year survival rate ranging from 50% to 70%. This is in sharp contrast to patients with metastatic tumor, whose five-year survival ranges from 0% to 5%. Nodal involvement alone carries an intermediate prognosis with five- and ten-year survival rates of 52% and 26%, respectively.[43] The prognostic significance of a tumor thrombus of the renal vein or vena cava is less clear. Although it appears that a subset of patients with venous extension alone may be cured by an appropriate surgical procedure, this feature is often associated with factors that adversely influence prognosis.[42,43] Patients whose tumors have a spindle cell pattern histologically have a poorer prognosis than those with other histologic types.[44]

Flow cytometric analysis of DNA ploidy has been used in an effort to identify other prognostic variables. Preliminary results from these studies suggest that renal cell tumor DNA ploidy is not an independent predictor of outcome.[45,46]

Approximately 25% of patients present with dissemi-

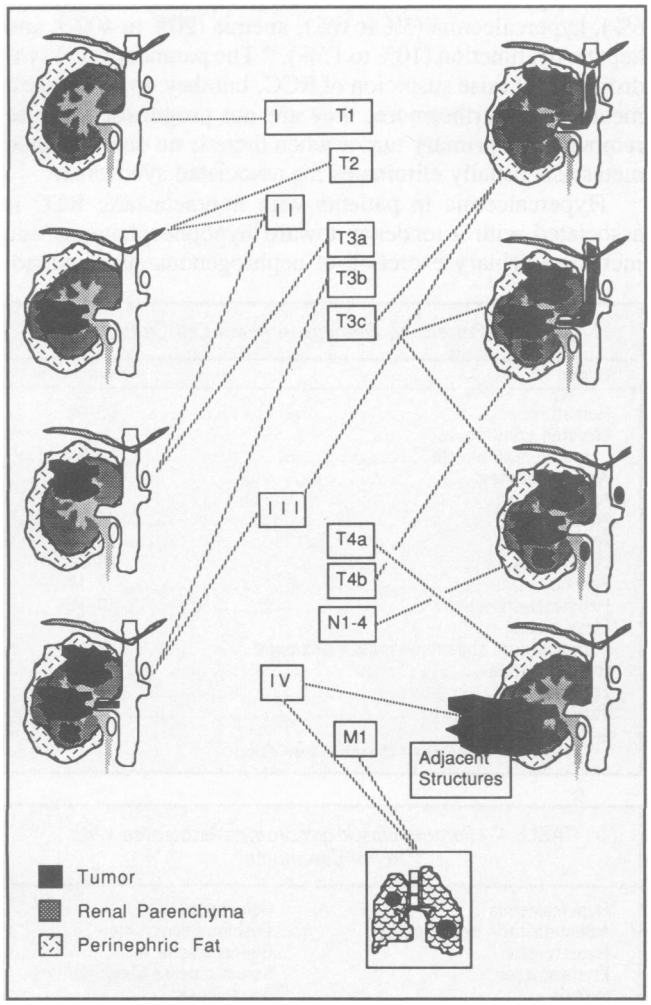

Figure 8.—Robson **(left column)** and TNM **(right column)** staging systems for renal cell carcinoma are depicted.

nated disease at the time of diagnosis, with an additional number manifesting metastasis after a nephrectomy.[3] With rare exceptions, the management of these patients is palliative or experimental. One exception is those patients who have a solitary surgically resectable metastasis temporally remote from their nephrectomy. Survival for five years has been reported in as many as 35% of these patients.[47]

Most patients with metastatic disease die despite treatment. Multiple chemotherapeutic and immunotherapeutic agents, alone or in combination, have been used in attempts to treat this neoplasm. Of 39 new agents evaluated in 2,120 patients from 1983 through 1989, a total response rate (either complete or partial) of 8.77% was observed.[48] This disappointing response rate may result in part from high levels of multiple drug resistance (MDR1) gene expression by these tumors.[49]

The success of biologic response modifiers, alone or in combination, is similar.[50] Initially there was enthusiasm for the combination of interleukin 2 and lymphocyte-activated killer cells based on the reported experiences at the National Cancer Institute. Subsequent multicenter trials, however, have failed to substantiate the initially reported 30% activity of this regimen.[51,52] Recombinant human interferon alfa, which has had an average total response rate of 16%, may represent a reasonable treatment option, particularly in view of its mild toxicity and ease of administration.[50]

Nephrectomy is of little use in treating a patient with metastatic disease.[53] Early reports, which suggested that nephrectomy might lead to a spontaneous regression of metastases, failed to establish cause or to consider surgical mortality. Most contemporary studies have failed to show any benefit from palliative nephrectomy in an otherwise asymptomatic patient. Patients with intractable pain, hematuria, retroperitoneal blood loss resulting from the primary lesion, or severe symptoms associated with a paraneoplastic syndrome may be considered for palliative nephrectomy. Angiographic renal artery embolization, and a variety of analgesic or anesthetic techniques, are usually preferable, however, given the mortality and morbidity associated with nephrectomy in these patients. Palliative nephrectomy is currently indicated only in patients who fail to respond to these measures or as adjunctive therapy as part of a prospective controlled clinical trial. Radiation therapy has not proved beneficial in a primary or adjuvant curative way. It is, however, useful in palliating symptoms attributable to locally recurrent or metastatic disease.[54]

Although the disease is varied in its individual behavior, the overall prognosis for patients with metastatic renal carcinoma is poor. Median survival rates for the "best risk" and "worst risk" groups are 12.8 months and 2.1 months, respectively.[55]

Nephroblastoma

Nephroblastoma (Wilms' tumor) is the most common malignant neoplasm of the urinary tract in children, accounting for 8% of all childhood tumors.[56] It is diagnosed in a third of the cases when the child is younger than 2 years and in two thirds of the cases when the child is younger than 4 years.

Clinical manifestations and diagnosis. The tumor is palpable in as many as 80% of cases and is often discovered by a parent. Pain is initially present in 50% of patients, hematuria (usually microscopic) in 10% to 20%, and hypertension in approximately 60%.[57,58] The diagnosis is usually established first by intravenous pyelography, which commonly shows caliceal distortion. Calcification within the mass occurs in 10% to 15% of patients. Abdominal ultrasonography or CT scans are useful to determine tumor extension and the possibility of involvement of both kidneys. This occurs in approximately 10% of patients. Arteriography is rarely used.

If the diagnosis remains uncertain after these studies are performed, the measurement of urine vanillylmandelic acid levels should help rule out neuroblastoma. Evaluation for the presence of metastases should be directed to the lungs, liver, and opposite kidney. A roentgenogram and CT scan of the chest and a CT scan of the abdomen are sufficient. Nephroblastoma, as with RCC, often produces a tumor thrombus in the inferior vena cava, which may have to be delineated by venacavography. Abdominal ultrasonography is also a reasonable alternative to establish this possibility.

Treatment. The development of a successful treatment for nephroblastoma is rightfully heralded as one of the most important advances in cancer therapy in the past few years. In the absence of distant dissemination or an unfavorable histologic finding, the prognosis has improved from a 25% survival rate in the 1960s to more than 90% currently.[59]

The initial treatment of nephroblastoma is complete surgical removal of the primary tumor and kidney even when there are metastases. A transabdominal approach provides the safest access and the necessary exposure of the liver, para-aortic nodes, and contralateral kidney for complete staging. Occasionally, radiotherapy or chemotherapy may be required preoperatively to decrease the bulk of massive tumors. Combined therapy is indicated postoperatively in all patients but is dependent on accurate staging, completeness of surgical extirpation, and tumor type. A tumor confined to the kidney in a child younger than 2 years requires only the postoperative administration of dactinomycin and vincristine sulfate, whereas in all others the best results are obtained with radiation therapy to the tumor bed plus the administration of dactinomycin and vincristine. Doxorubicin is also an active agent in treating this disease. Additional areas of current investigation are radiation therapy and the addition of doxorubicin to a regimen of vincristine and dactinomycin for patients with extensive local disease and favorable histologic appearance and radiation therapy with triple drug versus quadruple drug (addition of cyclophosphamide) for patients with unfavorable histologic type (anaplasia or sarcomatous elements). Wilms' tumor may occasionally be seen in adults; similarly, RCC occurs rarely in children.[60]

Tumors of the Renal Pelvis, Ureter, and Bladder

The urinary tract is lined with transitional epithelium from the level of the calices to the proximal urethra. Neoplastic processes arising from this lining account for more than 90% of all tumors involving the upper and lower urinary tract collecting systems.[61] This epithelium undergoes neoplastic transformation as a result of contact with carcinogens in the urine. Environmental carcinogens excreted in the urine come in intimate contact with the epithelial surface for prolonged periods of time, resulting in the classic induction and promotion phases associated with chemical carcinogenesis.[62] The diffuse nature of urothelial exposure to carcinogens often results in multifocal areas of dysplastic and neoplastic change.[63,64]

Uroepithelial neoplasms have a 4:1 male-to-female preponderance and typically occur in the sixth and seventh dec-

ade of life. There is, however, a broad range from the pediatric to the geriatric population. A number of environmental risk factors have been identified, including cigarette smoking, exposure to certain industrial chemicals, particularly aromatic amines, and long-term abuse of phenacetin-containing analgesics.[65-67]

The remaining 10% of tumors involving the urinary tract collecting system are composed of a diverse histologic group including squamous cell carcinoma, adenocarcinoma, and sarcoma. Squamous cell carcinoma probably arises from the transitional epithelium via the process of squamous metaplasia associated with chronic inflammatory changes. Indwelling foreign bodies (catheters) and parasitic infections involving the bladder wall (schistosomiasis) are associated with an increased risk of squamous metaplasia and neoplasia.[68,69]

Adenocarcinomas involving the urinary tract are typically limited to the urinary bladder. Although transitional epithelium may undergo adenomatoid metaplasia, most adenocarcinomas of the bladder are thought to arise from embryologic hindgut remnants such as a persistent urachus in the dome of the bladder.

Tumors of the Upper Urinary Tract

Transitional cell neoplasms involving the upper urinary tract account for less than 10% of urothelial tumors.[70] These lesions may occur anywhere along the course of the upper tract collecting system but most frequently in the distal ureter.[71] Hematuria remains the most common presenting symptom, occurring in as many as 80% of patients.[72] Although ureteral obstruction with superimposed hydroureteronephrosis will develop in 40% to 50% of patients, renal colic is rare because of the insidious onset of the obstruction.

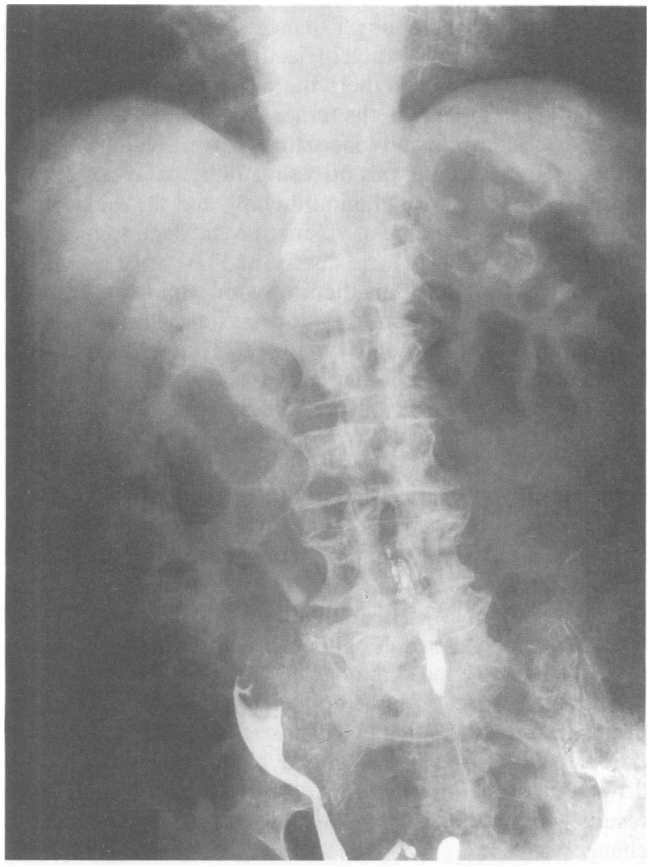

Figure 9.—A retrograde pyelogram shows the classic goblet sign caused by the intraluminal filling defect resulting from a ureteral transitional cell neoplasm.

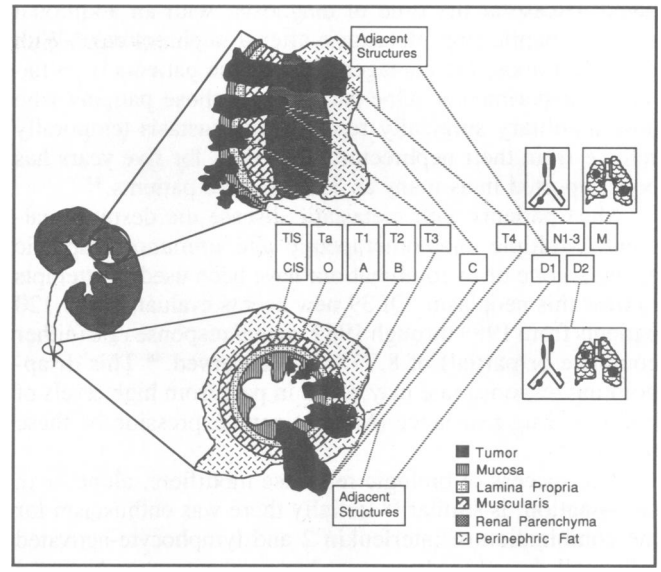

Figure 10.—The TNM **(upper)** and Jewett **(lower)** staging classifications for transitional cell neoplasms of the upper urinary tract are depicted.

Excretory urography followed by cystoscopy constitutes the initial diagnostic evaluation. In cases in which renal nonfunction secondary to long-standing obstruction precludes unilateral excretion of contrast medium, or when excretory urography is nondiagnostic, retrograde pyelography is the study of choice. Further evaluation may include cytologic studies of the upper urinary tract and direct visualization and biopsy with rigid or flexible ureteropyeloscopy. Care should be taken to exclude other radiolucent ureteral filling defects that include sloughed papillae, radiolucent stones, and fungus balls. Figure 9 shows the classic goblet sign, which is characteristic of ureteral transitional neoplasms.

Treatment is determined by the location, stage, and grade of the tumor and the status of the contralateral kidney. Chest radiograph, abdominal CT scan, and bone scan are necessary to determine the local and systemic extent of disease. Because of the difficulty in excluding local invasion, most patients with these lesions are treated with extirpative surgery. As a result of the unique propensity of these tumors for downstream metachronous recurrence, tumors involving the renal pelvis or calices, or both, have traditionally been treated with nephroureterectomy. Depending on the stage and grade, distal ureteral tumors may be amenable to local excision with subsequent ureteral implantation.[73] Highly selected groups of patients with unifocal, low-grade, low-stage neoplasms, or a contraindication to nephrectomy, have been managed successfully with endoscopic tumor ablation.[74]

The prognosis for these patients is stage- and grade-dependent. Figure 10 outlines the TNM and Jewett staging systems used for ureteral and upper tract transitional cell neoplasms. Fortunately, most are of low stage and grade and, therefore, have an excellent prognosis. Muscle invasion and direct local extension are poor prognostic signs.

The high rate of downstream metachronous tumor recurrence in these patients necessitates careful follow-up. Although a lesion develops in the contralateral upper urinary tract in less than 5% of patients, 50% to 60% of patients eventually have a bladder neoplasm.[75,76] For this reason, it is recommended that cystoscopy be carried out every three

months until the patient remains tumor-free for a period of a year. Semiannual or annual surveillance is then warranted.

The prognosis for patients presenting with or subsequently developing metastatic disease is poor. Recent improvements in the treatment of transitional cell carcinoma of the bladder using multidrug chemotherapy are promising, however, and support the use of these regimens in the treatment of disseminated transitional cell carcinoma of the upper urinary tract.[77]

Tumors of the Urinary Bladder

In 1992, approximately 50,000 new patients will present with tumors of the urinary bladder, 90% of which will have a transitional histologic appearance.[78] Hematuria is the most common presenting sign. When present, gross hematuria is typically total and painless. Irritative voiding symptoms, including frequency and dysuria, are additional common findings. Bladder irritability, with detrusor instability, represents a "final common path" response of the bladder to a spectrum of pathologic processes. Although this is commonly associated with bladder outflow obstruction due to prostatism, the clinician must be careful not to ascribe isolated symptoms of bladder irritability prematurely to prostatism in men in the age group at risk for both prostatism and urothelial malignancy.

The diagnostic workup is identical to that described for lesions of the upper urinary tract. Careful cystoscopy with urinary cytology is sufficient to preclude the presence of disease of the lower urinary tract. When identified, bladder abnormalities should be treated with transurethral excisional biopsy and bimanual bladder examination under anesthesia. Selected mucosal biopsies of adjacent areas of urethral abnormality may be necessary to define the presence of associated carcinoma in situ. For high-grade appearing lesions, and those involving the bladder neck, transurethral prostate biopsies are recommended to exclude prostatic duct or stromal involvement. The stage and grade of the tumor defined by excisional biopsy dictate further evaluation and therapy. Tumors are broadly divided into superficial and invasive categories. Figure 11 shows the TNM and Jewett classifications for neoplasms of the bladder. Tumors of T stage T1 or less are defined as superficial, with stage T2 or greater defined as invasive.

Superficial Bladder Carcinoma

Of patients with carcinoma of the bladder, 70% have superficial lesions at presentation.[79] The major disease-related issues for this group of patients can be divided into the risks of tumor recurrence and tumor progression.

The biologic behavior of superficial bladder carcinoma is characterized by polychronotropism, that is, multiple occurrences in space and time. One-year and overall recurrence rates of 56% and 70%, respectively, have been reported.[80,81] The cause of this exceptionally high rate of recurrence is unclear. Urothelial field change disease resulting from diffuse urothelial contact carcinogenesis clearly plays some role.[82] When metachronous recurrence rates of other organs at risk for diffuse contact carcinogenesis are compared, such as the nasopharynx, lungs, stomach, and colon, the bladder is unique in both the frequency and pattern of recurrence.[83-87] This finding is particularly striking considering the low grade and otherwise low malignant potential of most superficial bladder neoplasms.

Tumor implantation is a unique mechanism that may account for the idiosyncratic behavior of superficial bladder carcinoma.[88-92] Transurethral bladder tumor removal is novel in that it releases large numbers of viable tumor cells into a fluid medium in direct contact with areas of bladder

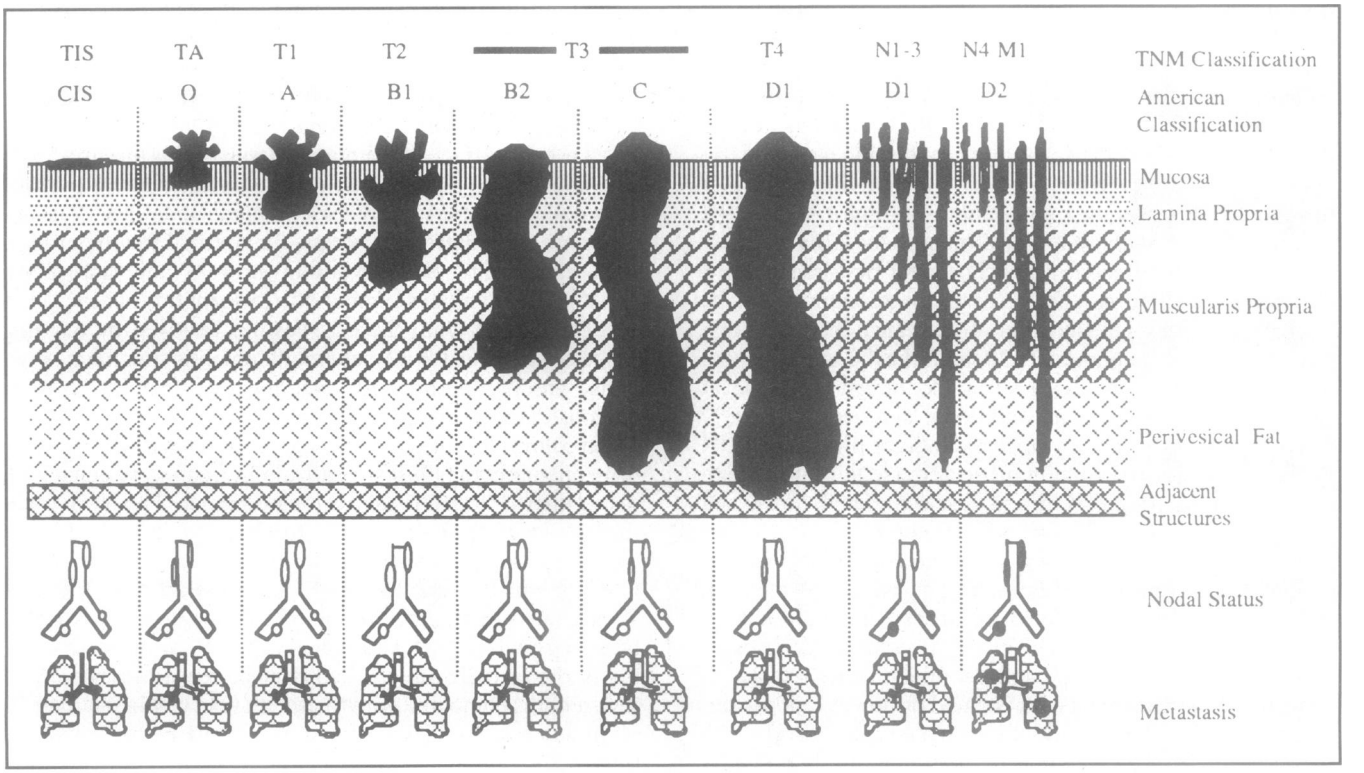

Figure 11.—The TNM (upper) and Jewett (lower) staging classifications for neoplasms of the bladder are shown.

injury. In vivo studies have shown that areas of urothelial injury represent preferential sites for tumor cell adherence and growth.[93,94] A number of iatrogenic and tumor-associated variables including concentration of tumor cells, surface area of urothelial injury, duration of urothelial exposure, and intravesical pressure at the time of exposure demonstrate a positive correlation with the size of the adherent inoculum.[95] The size of the adherent inoculum in turn determines the risk of tumor growth.

An additional iatrogenically mediated factor that may influence implantation-associated recurrence is the local milieu at the site of tumor cell adherence. Traumatic urothelial injury initiates the process of epithelial repair involving cell division, migration, and neovascularization. The same factors that regulate normal reparative processes may influence the growth of tumor cells adherent to the injury site.

To date, only tumor size and the number of tumors at presentation have correlated with risk of recurrence.[96,97] Bladder tumor recurrence is a cause of significant patient morbidity, but it is rarely life threatening. A subset of patients at high risk for recurrence based on their presentation may be treated in an effort to prevent recurrence, but usually therapy is withheld until the time of first tumor recurrence. Therapy to prevent recurrence is founded on the intravesical administration of chemotherapeutic or immunotherapeutic agents. Thiotepa, adriamycin, mitomycin, and bacillus Calmette-Guérin (BCG) vaccine have been administered in an effort to decrease recurrence rates.[98] In selecting an agent for intravesical therapy, the clinician must weigh not only the risk of recurrence but also the potential for disease progression as well as the toxicity associated with the chosen therapeutic agent. For patients with low-stage, low-grade lesions at low risk of progression, thiotepa represents a reasonable initial choice.

Tumor progression. The risk of tumor progression, defined as recurrence at a higher tumor stage, depends on initial tumor stage and grade. Although less than 2% of patients with grade 1, T0 lesions ultimately have disease progression, 69% to 83% of patients with grade 3 lamina propria invasion and associated carcinoma in situ have recurrence as muscle invasive disease.[99] Because disease progression is potentially fatal, careful attention must be paid to individual risks of patients for this phenomenon. Patients at high risk must be followed closely with cystoscopy, biopsy, and urinary cytology and the most effective agent chosen for first-line therapy. All patients at high risk for disease progression should be treated at the time of presentation. Intravesical BCG administered in six weekly courses of 120 mg is the therapeutic agent of choice. Patients failing a six-week induction course of BCG may benefit from an additional six-week course.[100] Maintenance BCG therapy appears to be of little benefit.[101] Patients in whom a second induction course fails are at high risk for tumor progression and disease-related death and should be considered for exenterative surgery.

Although it is categorized with the superficial bladder carcinomas, carcinoma in situ represents an aggressive form of urothelial neoplasia. Carcinoma in situ, either alone or in conjunction with papillary neoplasia, frequently progresses to muscle invasion and may represent the precursor lesion to invasive disease. Patients with isolated or mixed lesions containing carcinoma in situ should be treated aggressively with intravesical BCG at the time of presentation. Persistently positive cytologic studies of the bladder after therapy in the presence of negative results of mucosal biopsy of the bladder may indicate persistence of disease in the upper urinary tract or prostatic fossa.[102,103]

All decisions regarding the management of patients with superficial bladder carcinoma must be based on adequate biopsies of the bladder. The absence of muscle in the biopsy specimen suggests inadequacy of the specimen and the need for additional tissue.

Muscle Invasive Bladder Carcinoma

Tumor stages greater than or equal to T2 constitute invasive disease. The overall 50% disease-related mortality for patients with this stage of disease is indicative of its aggressive nature.[104] Treatment options are determined by the local extent of disease and the presence of systemic spread. The staging evaluation should include a chest radiograph, abdominal and pelvic CT scans, and a bone scan. If cystectomy is a consideration, the decision regarding concomitant urethrectomy and urinary diversion options depends on the degree to which the disease has extended into the prostatic fossa and proximal urethra. For this reason staging should include biopsies of these sites.

Treatment options for patients with organ-confined disease include radical radiotherapy or cystectomy. Data suggest that radical cystectomy confers the greatest likelihood of cure.[105] Advances in modern urologic oncology in the 1980s have greatly reduced the morbidity and mortality associated with radical cystectomy. Selected patients may be candidates for potency-sparing dissections.[106] New methods of continent urinary diversion afford improved body image and quality of life for both men and women.[107,108] Studies have failed to show additional benefit from preoperative adjuvant radiotherapy.[109]

Patients who refuse or are not medically fit to undergo radical cystectomy may benefit from definitive external beam radiation. Radiation therapy alone or in combination with a chemotherapeutic radiation sensitizer, such as fluorouracil or cisplatin, has been administered with curative intent.[110,111]

The identification of platinum-based regimens with activity against transitional cell carcinoma in the mid-1980s has had a notable effect on the management of this disease.[112,113] The role of these regimens in the management of patients with regionally confined disease remains undefined. The appropriate candidates for therapy, the optimal treatment regimen, the timing of drug administration (adjuvant versus neoadjuvant), and the number of treatment cycles have yet to be determined. Until these issues are resolved by ongoing multicenter clinical trials, chemotherapeutic treatment of patients with organ-confined transitional cell carcinoma must be considered experimental.

In contrast to patients with organ-confined disease, multidrug chemotherapy has a clear role in treating patients with disseminated transitional cell carcinoma. The two commonly used regimens with proven activity are MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) and CMV (cisplatin, methotrexate, and vinblastine). Total response rates ranging from 40% to 71% have been reported for these regimens.[113,114] Although most (>95%) patients eventually die of their disease, survival increases an average of four months compared with treatment with cisplatin alone.[115]

When treatment is administered in the neoadjuvant setting (before a planned cystectomy), a significant percentage (30%) of patients have been found to have no histologically

identifiable disease (stage P0) at the time of radical cystectomy. Unfortunately, attempts to define this patient population preoperatively have met with a significant incidence of understaging. In addition, carcinoma in situ, which is commonly associated with muscle invasive disease, is poorly responsive to currently used regimens and may represent a sanctuary lesion that predisposes to disease recurrence.[116] For these reasons, further studies will be necessary to determine the ability of neoadjuvant therapy to serve as a bladder-sparing treatment alternative.

Nontransitional Cell Bladder Neoplasms

Nontransitional cell bladder neoplasms account for less than 10% of all bladder tumors, with the most common histologic types being squamous cell, adenocarcinoma, and sarcoma. Squamous cell carcinoma and adenocarcinoma are commonly seen in adults and are usually invasive at presentation. These are aggressive radioresistant neoplasms that do not respond to drug regimens that proved efficacious against transitional cell lesions. Surgical extirpation of organ-confined disease at the time of presentation affords the greatest chance of cure.

Rhabdomyosarcomas of the prostate and bladder are unusual lesions observed in children. Therapy consists of surgical extirpation in combination with neoadjuvant and adjuvant combination chemotherapy. This multidisciplinary approach has afforded some improvement in the extremely poor prognosis for these patients.[117]

Summary

Neoplastic diseases of the kidneys and urinary collecting system are relatively common, but when detected early, they have an excellent prognosis. Because gross or microscopic hematuria may be an early harbinger of genitourinary pathology, the primary care physician and internist play an integral role in diagnosing these diseases. A high index of suspicion together with a thorough history, physical examination, and appropriate diagnostic studies will enable the correct diagnosis and improved patient management in most cases.

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